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Hyperuricemia in Patients with Type 2 Diabetes Mellitus at a Tertiary Care Hospital in Bahawalpur Pakistan

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ABSTRACT

Introduction: Hyperuricemia is linked to increased morbidity and diabetes complications, making early identification and treatment crucial for reducing the disease burden. Studies in Pakistan indicate variations in the prevalence of hyperuricemia among patients with type 2 diabetes mellitus (T2DM). **Objective:** To determine the prevalence of hyperuricemia in T2DM patients at a tertiary care hospital in Bahawalpur, Pakistan. **Material & Methods:** This retrospective study was conducted at Bahawal Victoria Hospital. T2DM was defined as HbA1c level of 6.5% or higher, a fasting plasma glucose level of 126 mg/dL or higher, or a 2-hour plasma glucose level of 200 mg/dL or higher during an oral glucose tolerance test. Hyperuricemia was defined as serum uric acid >7.0 mg/dl in males and >6.0 mg/dl in females. Exclusions included patients on thiazide diuretics, with malignancies, end-stage kidney disease, chronic liver disease, or pregnant women. Data from medical records of 240 T2DM patients were collected from March to August 2024, focusing on demographics, diabetes control, HbA1c levels, and complications. Statistical analysis was performed using SPSS version 23, applying Fischer's Exact test and Chi-Square test with $p < 0.05$ significance. **Results:** Mean age was 55.5+14.7 years, having a female preponderance (124, 51.7%). Mean diabetes duration was 7.1+5.6 years with the majority of patients having poor diabetes control (178, 74.2%). Nephropathy was seen in 27 (11.3%) and ischemic heart disease in 41 (17.1%). Hyperuricemia was present in 21 (8.8%) patients, showing significant association with diabetes duration and nephropathy. **Conclusion:** Hyperuricemia was not uncommon, with longer diabetes duration and the presence of nephropathy increasing the risk.

Keywords: Hyperuricemia, HbA1c, nephropathy, type 2 diabetes mellitus, uric acid

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INTRODUCTION

Type 2 Diabetes mellitus (T2DM) is a chronic disease characterized by hyperglycemia due to deficient insulin production or/and insulin resistance resulting in significant worldwide morbidity, impaired functional ability, poor life quality and mortality of the patients affected (1,2). The International Diabetic Federation estimates that approximately 537 million adults are affected by diabetes globally resulting in almost 6.7 million deaths in 2021, making diabetes a major health burden especially in low- and middle-income countries such as Pakistan where healthcare resources are already restrained (3,4). Abnormally high serum uric acid results in hyperuricemia. A byproduct produced in purine metabolism, uric acid acts as an anti-oxidant which protects atherosclerosis initially, but in advanced atherosclerosis uric acid acts as a pro-oxidant (5,6). In patients with diabetes, hyperuricemia had been linked to a poor prognosis with increased mortality and risk of developing diabetes complications such as nephropathy, retinopathy and neuropathy (7). Due to its role in atherosclerosis, Hyperuricemia also leads to various cardiovascular diseases including coronary artery disease (8,9). Recently, uric acid has also been linked with altered glucose consumption and the onset of T2DM, hypertension and chronic kidney disease (10,11).

The pathophysiology of hyperuricemia is postulated to be due to endothelial dysfunction, increased activity of renin-angiotensin-aldosterone system, inflammatory pathways and pro-fibrotic cytokine activation. These modulators contribute to advancements in micro-vascular complications of T2DM resulting in renal damage and nephropathy. A marked variation in prevalence of Hyperuricemia in T2DM has been reported in studies from Pakistan (12). From Peshawar, Ali et al. reported Hyperuricemia in 36.04% patients of T2DM, being linked to high risk of nephropathy (13). In Karachi, Raja et al. found Hyperuricemia in 39.9% males and 17.9% females (14). From Faisalabad, Shahid et al. demonstrated a significant link of hyperuricemia with diabetes mellitus, blood glucose, metabolic syndrome, decreased HDL-C and hypertension (15). Therefore, the present study was conducted to find out the frequency of hyperuricemia in patients with T2DM among Pakistani population.

The objectives of the study were to assess the prevalence of hyperuricemia in patients with T2DM within the Pakistani population and to examine the associations between hyperuricemia and various clinical variables, including diabetes duration, nephropathy status, gender, age, diabetes control, and ischemic heart disease. Additionally, the study aimed to identify demographic factors that may contribute to variations in hyperuricemia prevalence among T2DM patients in the local context. Ultimately, the findings were intended to enhance the existing body of knowledge regarding the relationship between hyperuricemia and type 2 diabetes, thereby potentially guiding future clinical practices and public health interventions. As Hyperuricemia is associated with elevated morbidity and risk of diabetes complications, identification of Hyperuricemia and its timely treatment will help to reduce the disease burden and mortality caused by it.

MATERIAL & METHODS

The present retrospective cross-sectional study was conducted at department of Medicine, Bahawal Victoria Hospital, Quaid-e-Azam Medical College Bahawalpur Pakistan to find out prevalence of Hyperuricemia in patients with type 2 diabetes mellitus. Type 2 Diabetes Mellitus was defined according to the American Diabetes Association (ADA) guidelines as HbA1c level of 6.5% or higher, a fasting plasma glucose level of 126 mg/dL or higher, or a 2-hour plasma glucose level of 200 mg/dL or higher during an oral glucose tolerance test, or previous history of diabetes diagnosis, or taking anti-hyperglycemic medicines (16). Hyperuricemia was defined as serum uric acid levels of more than for 7.0 mg/dl males and 6.0 mg/dl for females, or taking urate-lowering therapy (17). Nephropathy was labeled as presence of microalbuminria on urinalaysis, urine albumin creatinine ratio of 30–300 mg/g and eGFR of more than 60ml/min per 1.73 m2 (early nephropathy without evidence of end-stage/chronic renal disease to reduce risk of Hyperuricemia associated with renal dysfunction) (18). Ischemic heart disease was labeled as presence of acute myocardial infarction or unstable angina. Type 1 diabetes

mellitus was excluded through a combination of clinical history and laboratory findings: patients with a history of insulin dependency from diagnosis, evidence of autoimmune markers (such as positive islet autoantibodies), or a typical presentation of type 1 diabetes (e.g., younger age at onset and a rapid progression of symptoms) were identified and excluded from the study. Furthermore, patients using Hyperuricemia causing drugs such as thiazide diuretics and anti-tuberculous therapy; patients with malignancy or on chemotherapy; patients with end-stage kidney disease and chronic liver disease, and pregnant women were excluded from the study.

Keeping a confidence interval of 95% with a margin of error of 6%, a sample size of 239 was calculated using the expected frequency of Hyperuricemia as 33.72% in patients with type 2 diabetes mellitus (19). The present retrospective cross-sectional study was conducted in accordance with the ethical standards established in the 1964 Declaration of Helsinki, as revised in 2000. The study involved the assessment of medical records without any direct exposure to patients and Institutional ethical approval was waived off. Ethical approval and permission for data collection were obtained from the Head of the Department, ensuring that all procedures complied with institutional guidelines for research ethics. This allowed for the analysis of clinical data while maintaining patient confidentiality and minimizing ethical concerns related to direct patient interaction.

In this retrospective study, the parameters such as blood sugar levels, HbA1c, and uric acid levels were extracted from medical records and were required to be documented at the patient's most recent visit. Retrospective data of 240 patients with type 2 diabetes mellitus were included in the study using a non-probability consecutive sampling technique from March 2024 to August 2024. Data collection for the study was conducted using a structured data collection sheet specifically designed to capture relevant clinical and demographic variables. Trained healthcare professionals were responsible for gathering the data, ensuring consistency and accuracy. They collected information through medical record review and assessment, focusing on parameters such as age, gender, diabetes duration, HbA1c levels, diabetes control, nephropathy status, ischemic heart disease, and serum uric acid levels. This systematic approach aimed to minimize bias and facilitate a comprehensive analysis of the relationship between hyperuricemia and various risk factors in patients with type 2 diabetes mellitus. Incomplete records were excluded.

Statistical analysis: All the data was recorded and entered into SPSS version 23 for analysis. Mean and standard deviation were calculated for numerical data whereas percentage and frequency were generated for qualitative variables. Confounders and effect modifiers were controlled via stratification. Fischer's Exact test and Chi-Square test were applied post-stratification using p-value less than 0.05 as significant.

RESULTS

Medical records of 240 patients with type 2 diabetes mellitus were included in the present study. The mean age was 55.5+14.7 years with 139 (57.9%) patients aged 55 years or more, having a female preponderance (124, 51.7%) as shown in Table 1. The mean diabetes duration was 7.1+5.6 years with 128 (53.83%) patients having diabetes for 6 years or more as shown in Table 1. Mean HbA1c (%) was 9.2+2.6 and the majority of patients had poor diabetes control (178, 74.2%). Nephropathy was seen in 27 (11.3%) and ischemic heart disease in 41 (17.1%). In the present study, Hyperuricemia was present in 21 (8.8%) patients with type 2 diabetes mellitus.

Table 1: Clinical and demographic variables

Clinical and Demographic Variables		Frequency (n)	Percent (%)
Gender	Female	124	51.7
	Male	116	48.3
Age	54 years or less	101	42.1
	55 years or more	139	57.9
Diabetes Duration	5 years or less	112	46.7
	6 years or more	128	53.3
Diabetes Control	Good / Controlled	62	25.8
	Poor / Uncontrolled	178	74.2
Nephropathy	Absent	213	88.7
	Present	27	11.3
Ischemic Heart Disease	Absent	199	82.9
	Present	41	17.1
Hyperuricemia	Absent	219	91.3
	Present	21	8.8

Table 2 depicts the stratification of data with regards to Hyperuricemia to show a significant statistical association with diabetes duration (p-value 0.038) and nephropathy (p-value 0.009) but now with gender (p-value 0.698), age (p-value 0.591), diabetes control (p-value 0.764), or ischemic heart disease (p-value 0.143). Specifically, individuals with a diabetes duration of 6 years or more had a higher prevalence of hyperuricemia (16, 12.5%) compared to those with 5 years or less (05, 4.5%). Similarly, nephropathy was significantly associated, with 06 (22.2%) of patients with nephropathy exhibiting hyperuricemia compared to just 15 (7.0%) of those without it.

Table 2: Stratification of data with regard to Hyperuricemia

Clinical and demographic Variables	Hyperuricemia		p-value
	Absent (n 219)	Present (n 21)	
Gender:			0.698
Female	114 (91.9%)	10 (8.1%)	
Male	105 (90.5%)	11 (9.5%)	
Age:			0.591
54 years or less	91 (90.1%)	10 (9.9%)	
55 years or more	128 (92.1%)	11 (7.9%)	
Diabetes Duration:			0.038
5 years or less	107 (95.5%)	05 (4.5%)	
6 years or more	112 (87.5%)	16 (12.5%)	
Diabetes Control:			0.764
Good / Controlled	56 (90.3%)	06 (9.7%)	
Poor / Uncontrolled	163 (91.6%)	15 (8.4%)	
Nephropathy:			0.009
Absent	198 (93.0%)	15 (7.0%)	
Present	21 (77.8%)	06 (22.2%)	
Ischemic Heart Disease:			0.143
Absent	184 (92.5%)	17 (7.5%)	
Present	35 (85.4%)	06 (14.6%)	

DISCUSSION

An increasing global pandemic, diabetes mellitus has various non-modifiable and modifiable risk factors such as a sedentary lifestyle and obesity (20,21). Furthermore, obesity and diabetes are also related to a plethora of medical conditions such as atherosclerosis, metabolic syndrome,

hypertension, dyslipidemia and hyperuricemia which lead to an increased risk of complications affecting the renal, coronary and cerebral organ systems (11,22). The presence of hyperuricemia in T2DM can be explained by reduced uric acid excretion as a consequence of insulin resistance and hyperinsulinemia in addition to elevated purine production due to increased hexose monophosphate pathway shunt (23,24). Furthermore, citric acid accumulation results in phosphofructokinase inhibition, causing the cycle to redirect to increased production 6-phospho-gluconate and purine nucleotides, thereby elevating uric acid (25). Hyperuricemia plays a role in various pathological mechanisms in diabetes and its complications by causing endothelial dysfunction, increasing inflammation, inhibiting insulin pathway, enhancing oxidative stress, thrombus formation and renin-angiotensin-aldosterone system activation (26). Xu et al. found Hyperuricemia in T2DM to be significantly associated with poor prognosis, increased vascular complications, and cardiovascular mortality (27).

Alemayehu et al. reported that hyperuricemia was seen in 27.28% of patients of T1DM type 2 in the African continent with Central Africa having a higher prevalence (33.72%) as compared to North Africa (24.72%) but no differences were seen in comparison of patient gender (19). Different studies have reported different prevalence rates of Hyperuricemia in T2DM in different countries from as high as 32.6% in China (28) to 16.6% in Australia 16.6% (29). Arersa et al. demonstrated Hyperuricemia in 22.9% of T2DM patients being more common in old age, males, alcoholics, obese patients, and patients having prolonged diabetes duration (30). In the present study, Hyperuricemia was not an uncommon finding, seen in 8.8% patients of with type 2 diabetes mellitus. Furthermore, a statistical association of Hyperuricemia was found with diabetes duration and nephropathy but not with gender, age, diabetes control, or ischemic heart disease. This is markedly low when compared to various other studies depicting the prevalence of Hyperuricemia in T2DM from Pakistan (12). From Peshawar, Ali et al. reported Hyperuricemia in 36.04% of patients of T2DM, being linked to high risk of nephropathy (13). In Karachi, Raja et al. found Hyperuricemia in 39.9% of males and 17.9% of females (14). From Faisalabad, Shahid et al. demonstrated a significant link of hyperuricemia with diabetes mellitus, blood glucose, metabolic syndrome, decreased HDL-C and hypertension (15).

These national and international differences in the prevalence of Hyperuricemia in T2DM may be attributable to variations in environmental, economic, genetic and socio-cultural factors in addition to difference of cut-off values employed to label hyperuricemia, heterogeneity of participants enrolled, study design and awareness regarding risk factors of Hyperuricemia and T2DM. The differences in hyperuricemia prevalence among various Pakistani studies on type 2 diabetes mellitus (T2DM) can be attributed to several factors, including population characteristics, study timing, and laboratory methods. Variations in demographics, such as age and gender distribution, as well as regional lifestyle and dietary habits, significantly impact prevalence rates. Additionally, the temporal context of each study plays a role; changes in lifestyle factors and diabetes management over time can lead to differing results. Laboratory methods also vary, with different diagnostic criteria for hyperuricemia and varying testing techniques affecting serum uric acid measurements. Furthermore, the study design, whether cross-sectional or longitudinal, can influence findings as can the sample size and selection criteria. Socio-cultural factors, such as public awareness and education regarding diabetes and its complications, also contribute to discrepancies in reported prevalence. Collectively, these elements underscore the complexity of assessing hyperuricemia prevalence in T2DM across different studies in Pakistan.

There are some limitations of the present study. Being a retrospective study, it was limited to a single institution. Furthermore, we did not investigate the role of hypertension, obesity, smoking, and alcohol use. Therefore, the results may not be applicable to the general population. However, using the findings of our study, future prospective cohort or case-control studies should be planned to further highlight the role of Hyperuricemia in T2DM and its complications. Regular screening and prompt treatment of Hyperuricemia should be done in T2DM patients. Subsequently, good compliance with follow-ups

should also be ensured to reduce diabetes-related disease burden and improve life quality of these patients. There is also a need to enhance awareness regarding lifestyle modifications, physical activity, and healthy behavior among T2DM patients.

CONCLUSION

Hyperuricemia was not an uncommon finding in our study, seen in 8.8% patients of type 2 diabetes mellitus. Furthermore, a statistical association of Hyperuricemia was found with diabetes duration and nephropathy but not with gender, age, diabetes control, or ischemic heart disease. Regular screening and prompt treatment of Hyperuricemia should be done in T2DM patients. Subsequently, good compliance with follow-ups should also be ensured to reduce diabetes-related disease burden and improve life quality of these patients.

Author declaration

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None.

Authors' contributions:
Conceptualization and Design: NIB, MSAG, BW; Methodology: NIB, MSAG, BW; Data collection and Patient Care: MSAG, DS; Literature Review: NIB, MH, BW; Data Analysis and Interpretation: NIB, BW.; Writing - Original Draft: NIB, MSAG, BW; Writing - Review & Editing: DS, MH; Supervision: NIB.

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The authors declare that there is no financial or non-financial conflict of interest.

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The present retrospective cross-sectional study was conducted in accordance to the ethical standards laid down in the 1964 Declaration of Helsinki, revised in the year 2000. The present study was based on assessing medical records only with no direct exposure to the patients. Permission for data collection and ethical approval was obtained from the Head of the department.

Statement on data availability:
Data generated or analyzed during this study are available from the corresponding author upon reasonable request.

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